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Are SK Channels a Logical Target for Treating Ventricular Arrhythmias? First, do no harm...

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Advances in the use of selective ion channel blockers in the pharmacologic treatment of cardiac arrhythmias in the past half century have been slow, incremental and bumpy. The CAST trial made evident the danger of suppressing ventricular ectopy using selective sodium channel blockers in the setting of ischemic heart disease (1). While selective hERG channel blockers are used for the treatment of atrial fibrillation, the risk of Torsade de Pointes associated with these drugs is well recognized, and all new drugs are now screened for interaction with this channel and risk of ventricular proarrhythmia. In the current issue, Chang and Chen review the evidence for the use of selective calcium-activated potassium channel blockers in the treatment of ventricular arrhythmias (2).

Since they are activated in response to elevated intracellular calcium levels, calcium activated potassium channels (SK channels) have the potential to link repolarization to calcium influx. While calcium influx is a critical process for the activity of cardiac myocytes, SK channels are widely distributed, also expressed in the endothelium, smooth muscle cells, central and peripheral neurons. The discovery of SK channels was based in part on the recognition of the blockade of these channels by the bee venom toxin apamin. The SK channel family has at least 3 prominently expressed members, SK1, SK2 and SK3, each with a different sensitivity to apamin. There may be a role for different splice variants of these channels expressed in different tissues and/or pathophysiologic conditions. SK channels colocalize with L-type calcium channels in the heart, and sense intracellular calcium release from the sarcoplasmic reticulum.

Studies based on use of apamin to assess the impact of SK channels on cardiac electrophysiology have yielded confusing results, based on differences in the response of different species, cardiac chamber and cardiac function. Typically, apamin sensitive currents have been larger in healthy atrial than in ventricular myocytes, with little if any action potential prolongation detected in response to apamin in healthy ventricular myocytes. The pharmacology and function of these channels is complex, and the recent development of additional blockers seems likely to help resolve some of the issues associated with understanding the species-, chamber- and disease specific variations in IKAS current and

distribution. Bonilla reported increased expression of SK2 and SK3 protein in the atria and ventricle of a canine HF model and in the atria and ventricles of heart transplant recipients (3). Interestingly, the currents in atrial myocytes of failing hearts no longer responded to apamin. Differences in the pharmacology of these channels has been associated with likely differences in the drug sensitivity of homomeric (eg. SK2) versus heteromeric (eg., SK2/SK3) subunit assembly (4).

Abnormal intracellular calcium cycling is a hallmark of atrial and ventricular arrhythmogenesis (5). Chua, et al. previously reported that apamin-sensitive current density (I_{KAS}) is increased in epicardial myocytes from failing rabbit hearts, with increased sensitivity to intracellular calcium (6) They have also reported a similar increase in I_{KAS} density in endo- and epicardial myocytes of failing human hearts, along with increased expression of SK2 protein in those hearts. Bonilla and colleagues have confirmed the increase in I_{KAS} in both a canine model of chronic heart failure and in the explanted hearts of end-stage heart failure patients undergoing transplant procedures (3).

Are SK channels good targets for treatment of ventricular arrhythmia? Chua and colleagues demonstrated that apamin treatment suppressed post-shock shortening of action potential duration in rabbits that had experienced ventricular fibrillation (6). While this is potentially a useful response, action potential prolongation carries a pro-arrhythmic risk for initiation of ventricular fibrillation. Given the diminished repolarization reserve in heart failure, and the intrinsic heterogeneity associated with repolarization and conduction velocity in the failing heart, selective pharmacologic suppression of I_{KAS} is not an obvious choice as a first line therapy. Chang and Chen recognize the significant risk of pro-arrhythmia associated with changes in SK channel expression in the setting of AV block and other conditions (2). Bonilla and colleagues conclude that I_{KAS} blockade for treatment of AF is not warranted in the setting of HF, due to the increased risk of ventricular proarrhythmia (3).

Abnormalities in intracellular calcium release and reuptake contribute to electrical alternans; the threshold for alternans is reduced in failing hearts and contributes to the increased risk of ventricular tachycardia and fibrillation (7). It seems likely that increased and heterogeneous expression of SK channels in the failing heart contributes to the regional variations that promote action potential alternans. Does this mean that it is logical to block SK channels in an effort to prevent ventricular arrhythmias? When considering drug targeting, it is useful to recall the most fundamental precept of medicine: *Primum non nocere* – first, cause no harm. Given the diversity of cell types and physiologic processes that are affected by SK channels, the potential for off-target effects seems great. Chang and Chen urge continued research into the clinical evaluation of SK channel blockers and remain cautiously optimistic about their potential clinical utility. I concur with the need for mechanistic studies, but suggest that current evidence supports a greater need for caution than optimism.

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